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(54) Title: HYDROGEL FOR THE THERAPEUTIC TREATMENT OF ANEURYSMS

(57) Abstract

The hydrogel for the treatment of aneurysms acts as a carrier for both a radiopaque agent allowing the hydrogel to be visualized under fluoroscopy and a therapeutic agent such as one or more human growth factors. The hydrogel is delivered through a catheter into the aneurysm, where the hydrogel becomes more viscous upon reaching body temperature, or upon exposure to bodily fluids, to block blood flow into the aneurysm. In addition to stopping blood flow into the aneurysm, the delivery of human growth factors to the aneurysm site promotes the growth of a cellular layer across the neck of the aneurysm. The hydrogel may be of a type that dissolves over time or one which remains as a permanent occlusive agent within the aneurysm.

HYDROGEL FOR THE THERAPEUTIC TREATMENT OF ANEURYSMS

BACKGROUND OF THE INVENTION

Field of the Invention:

This invention relates generally to treatment of vascular aneurysms, and more particularly concerns the use of hydrogels for use in occluding aneurysms and in controlled drug delivery for treatment of aneurysms.

Description of Related Art:

Aneurysms have been traditionally treated with externally placed clips, or internally by detachable vasoocclusive balloons or an embolus generating vasoocclusive device such as one or more vasoocclusive coils. The delivery of such vasoocclusive devices can be accomplished by a variety of means, including via a catheter in which the device is pushed through the catheter by a pusher to deploy the device. The vasoocclusive devices can be produced in such a way that they will pass through the lumen of a catheter in a linear shape and take on a complex shape as originally formed after being deployed into the area of interest, such as an aneurysm. In current techniques, the vasoocclusive devices take the form of spiral wound wires that can take more complex three dimensional shapes as they are inserted into the area to be treated. By using materials that are highly flexible, or even super-elastic and relatively small in diameter, the wires can be installed in a micro-catheter in a relatively linear configuration and assume a more complex shape as it is forced from the distal end of the catheter.

Adhesives that have been introduced to help heal aneurysms include cyanoacrylates, gelatin/resorcinol/formol, mussel adhesive protein and autologous fibrinogen adhesive. Fibrin gels have also been used as sealants and adhesives in surgery, and hydrogels have been used as sealants for bleeding organs, and to create

and to promote healing of the diseased vasculature, in a manner that can be visualized under fluoroscopy. The present invention meets these and other needs.

SUMMARY OF THE INVENTION

The present invention solves these and other problems by providing, in its broadest aspect, an improved method for treating an aneurysm by delivering a hydrogel carrying growth factors to promote cellular growth across the neck of the aneurysm, to eliminate and heal the aneurysm with the body's own cellular growth. In addition to delivering the growth factor, the hydrogel acts as an embolic agent blocking the flow of blood into the aneurysm and eliminating the chance for hemorrhage, and can be used either separately, or in combination with other occlusive, embolus generating devices in treatment of aneurysms.

Briefly, and in general terms, a presently preferred embodiment of the present invention provides for a method for the treatment of aneurysms non-mechanically, through the delivery of human growth factors and/or gene therapy to the site of an aneurysm. The invention utilizes a hydrogel that acts as a carrier for both a radiopaque agent allowing the hydrogel to be visualized under fluoroscopy and a therapeutic agent such as one or more human growth factors. The hydrogel is delivered through a catheter into the aneurysm, where, in one currently preferred embodiment, the hydrogel becomes more viscous upon reaching body temperature, or upon exposure to bodily fluids. In our presently preferred embodiment, the hydrogel is constituted so as to remain a liquid at temperatures below about 37°C, to thereby facilitate the placement and retention of the gel and gel contained agents within the aneurysm. The hydrogel preferably then solidifies to block blood flow into the aneurysm. In addition to stopping blood flow into the aneurysm, the delivery of human growth factors to the aneurysm site promotes the growth of a cellular layer across the neck of the aneurysm. The hydrogel may be of a type that dissolves over time or one which remains as a permanent occlusive agent within the aneurysm.

These and other aspects and advantages of the invention will become apparent from the following detailed description.

oligoglycolylacrylates, such as described in U.S. Patent 5,626,863, which is incorporated by reference herein; carboxy alkyl celluloses, including but not limited to carboxymethyl cellulose; partially oxidized cellulose; biodegradable polymers including but not limited to polymers and oligomers of glycolide, lactide, polylactic acid, polyesters of α-hydroxy acids, including lactic acid and glycolic acid, such as the poly(α-hydroxy) acids including polyglycolic acid, poly-DL-lactic, poly-L-lactic acid, and terpolymers of DL-lactide and glycolide; ϵ-caprolactone and ϵ-caprolactone copolymerized with polyesters; polylactones and polycaprolactones including poly(ϵ-caprolactone), poly(δ-valerolactone) and poly(gamma-butyrolactone); polyanhydrides; polyorthoesters; other hydroxy acids; polydioxanone; and other biologically degradable polymers that are non-toxic or are present as metabolites in the body; as well as non-degradable polymers such as styrene and acrolein.

Collagen-hydroxyethyl-methacrylate (HEMA) hydrogel polymer is commonly formed from a gelled and crosslinked hydrophilic monomer solution to form a three dimensional polymeric meshwork anchoring macromolecules. Crosslinking of the hydrophilic monomer solution can be accomplished by free radical polymerization of hydrophilic monomers, such as hydroxyethyl-methacrylate (HEMA). Hydrogel polymers formed by free radical polymerization of monomer solutions require crosslinking to form the three dimensional network to gel the aqueous solution. HEMA monomer solutions typically can be crosslinked to gel by dimethacrylate, although other crosslinking agents, such as ethylene glycol dimethacrylate or methylmethacrylate, can also be used during polymerization to modify the hydrogel. A wide variety of other hydrophilic monomers may also be suitable for purposes of the invention.

Inorganic gels from which the hydrogel of the invention can be selected include, by way of example and not by way of limitation, silica, alumina, and ferric oxide. In addition, an adhesive can be introduced via a catheter to initially help seal the neck of an aneurysm, and can be selected from the group consisting of cyanoacrylates, gelatin/resorcinol/formol, mussel adhesive protein and autologous fibrinogen adhesive. It should thus be apparent that the hydrogel of the invention can be of a type that dissolves over time or one that remains as a permanent occlusive agent within the aneurysm.

WHAT IS CLAIMED IS:

1. A method for treating an aneurysm, the aneurysm having a dome portion and a neck opening into a parent vessel, the method comprising the steps of:

delivering a hydrogel into the dome portion of the aneurysm and adjacent to the neck of the aneurysm, the hydrogel containing a radiopaque material and a therapeutic agent that is released from the hydrogel in the aneurysm to promote cellular growth within the aneurysm to occlude at least a portion of the neck of the aneurysm.

2. The method of Claim 1, wherein said hydrogel is selected from the group consisting of organic gels and inorganic gels.

3. The method of Claim 1, wherein said hydrogel is selected from the group consisting of biodegradable polymers and non-degradable polymers.

4. The method of Claim 1, wherein said hydrogel is selected from the group consisting of gels formed from polysaccharides, mucopolysaccharides, polyaminoacids, proteins that support cell growth and healing, polyphosphazines, polyphosphoesters, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, polyvinylpyrrolidone, polyethyloxazoline, polyethylene oxide-co-polypropyleneoxide block copolymers, PGA-PEG-PGA block copolymers, PGA-PEG diblock copolymers, acrylates, carboxy alkyl celluloses, partially oxidized cellulose, polymers and oligomers of glycolide and lactide, polylactic acid, polyesters of α-hydroxy acids, polylactones, polycaprolactones, polyanhydrides, polyorthoesters, polydioxanone, styrene, acrolein and combinations thereof.

5. The method of Claim 1, wherein said hydrogel is selected from the group consisting of gels formed from hyaluronic acid, dextran, heparin sulfate, chondroitin sulfate, heparin, agar, starch, alginate, fibronectin, gelatin, collagen, fibrin, pectins, albumin, ovalbumin, collagen-hydroxyethyl-methacrylate (HEMA);

hydrogel into the dome portion of the aneurysm and adjacent to the neck of the aneurysm, the hydrogel containing a radiopaque material and a therapeutic agent that is released from the hydrogel in the aneurysm to promote cellular growth across the neck of the aneurysm to close the neck of the aneurysm.

12. The method of Claim 11, wherein said hydrogel is selected from the group consisting of organic gels and inorganic gels.

13. The method of Claim 11, wherein said hydrogel is selected from the group consisting of biodegradable polymers and non-degradable polymers.

14. The method of Claim 11, wherein said hydrogel is selected from the group consisting of gels formed from polysaccharides, mucopolysaccharides, polyaminoacids, proteins that support cell growth and healing, polyphosphazines, polyphosphoesters, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, polyvinylpyrrolidone, polyethyloxazoline, polyethylene oxide-co-polypropyleneoxide block copolymers, PGA-PEG-PGA block copolymers, PGA-PEG diblock copolymers, acrylates, carboxy alkyl celluloses, partially oxidized cellulose, polymers and oligomers of glycolide and lactide, polylactic acid, polyesters of α-hydroxy acids, polylactones, polycaprolactones, polyanhydrides, polyorthoesters, polydioxanone, styrene, acrolein and combinations thereof.

15. The method of Claim 11, wherein said hydrogel is selected from the group consisting of gels formed from hyaluronic acid, dextran, heparin sulfate, chondroitin sulfate, heparin, agar, starch, alginate, fibronectin, gelatin, collagen, fibrin, pectins, albumin, ovalbumin, collagen-hydroxyethyl-methacrylate (HEMA); diacrylates, oligoacrylates, methacrylates, dimethacrylates, oligomethoacrylates, PEG-oligoglycolylacrylates, carboxymethyl cellulose, polyesters of lactic acid, polyesters of glycolic acid, poly(α-hydroxy) acids including polyglycolic acid, poly-DL-lactic, poly-L-lactic acid, and terpolymers of DL-lactide and glycolide, ϵ-caprolactone, ϵ-caprolactone copolymerized with polyesters, poly(ϵ-caprolactone), poly(δ-

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/30 A61K47/32 A61K47/34 A61K47/36 A61K47/38
A61K38/18 A61K38/20 A61K39/395 A61K33/24 A61K47/02
//(A61K38/18,33:24),(A61K38/20,33:24),(A61K39/395,33:24)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	abstract ---	1-20
Y	EP 0 547 530 A (FORD HENRY HEALTH SYSTEM) 23 June 1993 (1993-06-23) column 6, line 24-39; claims ---	1-20
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Y	US 5 580 568 A (EVANS SCOTT ET AL) 3 December 1996 (1996-12-03) abstract ---	1-20
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[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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